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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CROWELL & MORING LLP
Intellectual Property Group
P O Box 14300
Washington, DC 20044-4300

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,414	SZYF ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09/22/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Reply under 37 CFR §1.111 and Rule 132 Declaration filed May 10 are acknowledged. Amendments to the claims have been entered as requested. Claims 1-31 were previously canceled; claims 37 and 38 are currently canceled. Claims 32, 33, 35 and 36 are amended. Claims 32-36, and 39-40 are pending. Claims 32-36 are the subject of this Office action; claims 39-40 are withdrawn from examiner's consideration as directed to the non-elected invention.

DETAILED ACTION

1. Objections

1.1. Claims

Amended claim 32 and dependent claims 33-36 are withdrawn from consideration in part regarding SEQ ID NO: 4, 6, and 8. The currently amended claim 32 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons. Original claim 32 was directed to the method of inhibition of tumorigenesis by inhibiting human demetylase consisting amino acids 150-411 of SEQ ID NO:2, which is a human demetylase disclosed by Applicants. The scope of the currently amended claim is broader than the scope of the elected claim 32, which was a subject of previous Office Actions. The scope includes homologs of SEQ ID NO:2 which are: human SEQ ID NO: 4, and two mouse sequences SEQ ID NO:6 and 8. SEQ ID NOs: 4, 6 and 8 are not disclosed as actually having demethylase activity, and were not elected by Applicants, and not examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, amended claim 32 and dependent claims 33-36 are withdrawn from consideration in part regarding SEQ ID NO: 4, 6, and 8, as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

1.2. Drawings

The response to objection to drawings and legends, as well as amendments to the specification are acknowledged. Objections are withdrawn.

2. Rejections

1.2. 35 USC, section 112, second paragraph

Rejection of claims 37-38 made in the last Office Action is moot because the claims have been cancelled.

The amended claim 32 is rejected as being unclear in recitation "wherein production of DNA demethylase is increased in comparison with that of a non-tumor cell". The phrase appear to be a step in the method and not a definition of the characteristics of the tumor cell being treated. To overcome this rejection the examiner suggests the following amendments:

in the first line, after the word tumorigenesis insert "in a tumor cell",

in the second line, after the word demethylase insert "in said tumor cell".

Rejection of claim 36 for insufficient antecedent is withdrawn, because the claim has been amended.

Rejection of claim 35 because of recitation of the phrase "an antisense oligonucleotide of DNA demethylase or an imidazole derivative thereof" is withdrawn because the claim has been amended.

Rejection of Claim 32 and dependent claims 33-36 because claim 32 recites the tem "a homologue thereof" is withdrawn because the claim has been amended.

2.2. 35 USC, section 112, first paragraph

2.2.1. Lack of written description

Rejection of claim 32 for lack of structural description of dMTase homologs, made in the office Action of Jan. 09, 2004, is withdrawn because the claim has been amended. However as indicated above, claim 32 in part directed to SEQ ID NO: 4, 6, and 8 is an invention that is independent or distinct from the invention originally claimed and therefore is not the subject of the examination.

Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for inhibiting tumorigenesis by altering methylation pattern in a patient DNA, i.e., in vivo, by any inhibitor of dMTase, or an

inhibitor which is a double stranded C^mG oligonucleotide, by an antisense oligonucleotide and imidazole and its derivatives, wherein dMTase consists of amino acids 150—411 of SEQ ID NO: 2. Applicants have failed to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

The term tumorigenesis is generic and encompasses many phenomena related to onset of carcinogenic transformation and progression of tumor. Thus, the claim is directed to a genus of methods directed to inhibition of many phenomena (species) of tumorigenesis. It is unclear to which of this phenomena Applicants are referring to. Fig. 14 and 15 provide some data on inhibition of colony formation by tumor cells in soft agar. The feature of the colony formation in soft agar is only one of many features of tumorigenesis, and the only species provided by applicants is not representative of all the other species, i.e. of all phenomena related to carcinogenesis. Furthermore, the specification fails to provide any evidence that treatment with imidazole inhibits growth of any tumor cells as claimed in claim 35.

The application is silent as to the methylation pattern of any gene in any patient and its alteration in comparison with a healthy person at the beginning and at the end of treatment; particularly there is no correlation in changes of methylation pattern and silencing of any gene as claimed in claim 36. Applicants even do not disclose any methylation pattern for any gene in human A549 lung cancer cells used in the agar growth test. This is a complete lack of written description.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. The written description requirement is satisfied by the disclosure of the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem*. 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as words, figures or diagrams presenting the recited biological phenomena and their changes. Given this lack of sufficient written description of tumorigenesis phenomenon to be inhibited, and of alteration of any methylation pattern in a patient by use of inhibitor of DNA demethylase one skilled in the art is not convinced that inventors had possession of the claimed invention at the time the application was filed.

In addition, the method of claim 32 uses any antagonist or inhibitor of DNA demethylase. The terms antagonist or inhibitor are generic terms the scopes of which cover large and variable chemical compounds. The Applicants teach only the following representatives of the claimed genus: oligonucleotide consisting of 4 units C^mG, wherein these four units may be repeated several times, anti-DNA demethylase antibody, an antisense oligonucleotide of DNA demethylase and imidazole. In addition, the structure of the antisense oligonucleotide of DNA demethylase is not described in

details, because the antisense vector of Fig. 15 is depicted schematically. This description is insufficient to give the identifying characteristics of all inhibitors as broadly recited by the claim. Given the lack of structural characteristics of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claim 36 is rejected because the claim is directed to a method of inhibition of tumorigenesis by alterating metylation of pattern in a patient DNA, wherein the alteration of the pattern silences a gene. Applicants' attention is turning to the fact that the specification is silent about any gene that is to be silenced and for that reason the specification does not teach any correlation in changes of methylation pattern and silencing of a gene as claimed in claim 36. More importantly, in case of a tumor suppressor gene inhibiting demethylase may lead to excessive methylation of its promoter region and transcriptional inactivation; see the abstract of the exhibit D attached to the reply of May 10, 2004. In result, tumorigenesis in its early steps may evolve to a metastatic from. Acceleration of tumorigenesis is not the intended use of a dMTases inhibitor.

On page 42 of the specification Applicants teach that high levels of dMTase are expressed in murine carcinoma cell line Y1 that bears a 30 fold amplification of Ha-ras (an activated gene). However, the specification fails to teach that the growth of Y1 cells *in vivo*, or even in vitro, was inhibited because metylation of Ha-ras was increased due

to inhibition of dMTase. In conclusion, because the Applicants did not describe any gene whose silencing is related to inhibition of tumorigenesis, one skilled in the art is not convinced Applicants were in possession of the claimed invention when the application was filed.

2.2.2. Scope of enablement

Claim 32-36 were rejected in the previous Office Action for lack of enablement. Rejection of claims 37-38 is moot because the claims have been cancelled.

The amended claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of colony formation of tumor cells in vitro by some inhibitors of dMTAse, like CmG and oligonucleotides being their repetitions does not reasonably provide enablement for inhibition of tumorigenesis in a patient, i.e. in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 32 is directed to a method for inhibition of tumorigenesis in a patient having a tumor in which production of DNA demethylase is increased, using any inhibitor of dMTAse. The specification, however, fails to teach inhibition of growth of any tumor in a patient or in vivo model of tumor growth. The specification teaches colony formation by tumor HEK 293 cells *in vitro* (Fig. 15) transformed with a plasmid containing an antisense dMTase oligonucleotide, or colony formation by unknown cells (Fig. 14) that is inhibited by meCpG. Applicants fail to describe any other inhibition of

tumor cell growth by any other inhibitor, including imidazole, which has been shown to inhibit dMTase catalytic activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses inhibition, of any phenomenon related to tumorigenesis, of any tumor with enhanced dMTase in any patient. The one skilled in the art realizes that mechanisms underlying tumorigenesis are versatile and not every tumorigenesis is caused by demethylation of cytosine in CG islands, which may lead to derepression of some genes involved in carcinogenesis (oncogenes). The example of the mechanism of tumorigenesis not related to methylation or demethylation of the patient's DNA is deletion or mutation in one of tumor suppressor genes. Therefore, not all tumors that have increased dMTase activity would regress after treatment with demethylase inhibitors.

In conclusion, without further guidance on the part of Applicants as to the details regarding phenomenon involved in tumorigenesis of a definite type of tumor,

experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

Dependent claims 33-36 are included in this rejection because they do not correct the language of the base claim.

In addition, claim 32 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition by meCpG, imidazole, and dMTAse antibodies, does not reasonably provide enablement for inhibition by any inhibitor of dMTAse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses inhibition by any inhibitor of dMTAse, of any phenomenon related to tumorigenesis a of tumor when wherein production of DNA demethylase is increased.

The state of art of inhibiting tumorigenicity by inhibitors of dMTASE is in early stage, therefore unpredicatability in the art is high. The claim is directed to the use of any known and unknown inhibitor of dMTAse in a patient. However the in vitro inhibitors disclosed by Applicants are not representative species of the genus of dMTAse inhibitors which certainly include chemical compounds of different structure whose metabolism and toxicity in patients' body are unknown. Although enablement is not precluded by screening many chemical agents, when the number of potential inhibitors is large the Applicants should provide sufficient guidance regarding their chemical structure. Without such guidance experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

2.2.3. Lack of enablement

Amended claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 32 is directed to a method of inhibition of tumorigenesis by an antagonist or inhibitor of DNA demethylase wherein methylation pattern in a patient DNA is altered. Claim 36 recites alteration of the methylation pattern that silence a gene. The

specification, however, fails to teach what is DNA methylation pattern in a patient and how to alter it, or how to alter it to silence any gene. Thus, to make and use the claimed invention necessitates undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses alteration DNA methylation pattern in a patient suffering from tumor wherein production of DNA demethylase is increased or alteration the methylation pattern to silence any gene. However, Applicant does not provide any teaching of what this pattern is in bulk tumor DNA or in its particular gene or how to alter the methylation pattern so that growth of the tumor were inhibited. There is no guidance as to what the pattern of DNA methylation should be in a healthy tissue and its tumor counterpart and how to visualize it. Applicants only provide the guidance how to measure the overall demethylase activity but not the pattern of DNA methylation. There is no a single measurement of percentage of cytosine methylation for any single gene. Those skilled in the art know that the pattern of DNA methylation is different in different genes, depending on the nucleotide sequence and the state of cell differentiation or physiological state of the cell from which the gene is isolated.

In conclusion, without further guidance on the part of Applicants as to the details regarding the measurement and visualization of methylation pattern and alteration in the methylation pattern required to inhibit tumor growth, experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

Dependent claims 33-35 are included in this rejection because they do not correct the language of the base claim.

3. Applicants arguments and examiners answers

3.1. 35 USC section 112, first paragraph, lack of written description

Traversing the rejection, Applicants in their Remarks write on page 9, line 2:

> "In support of the fact that the Applicants were in possession of the claimed invention at the time the application was filed, Applicants present the articles of Slack et al. (2002) J. Gene Med., 4, 381-389 as Exhibit A, Ivanov et al. (J. Gene Med., 5, 893-899, as Exhibit B, and Campbell et al. (2004) Carcinogenesis, 25(4): 499-507, as Exhibit C, which show that inhibition of demethylase (SEQ ID NO: 2) by an antisense molecule inhibits tumorigenesis in vivo. All of the above published data came as a direct result of the present application."

Applicants' arguments have been fully considered but are found not persuasive. The claims of the instant application are directed to *in vivo* method of inhibition of tumorigenesis wherein DNA methylation pattern is changed in result of treatment.

However the specification lacks any in vivo data and for that matter written description of the invention as claimed. The filed Exhibits are publications containing *in vivo* data that were obtained several years after filling the instant Application, which is a national stage of the PCT/CA98/01059, filed 11/12/1998.

In addition, Exhibits A, B, and C do not cover any inhibitor or inhibitors described in the instant specification, but oligonucleotides of structure and S-adenosylmethionine that are not disclosed in the instant specification. Neither the Exhibits teach a methylation pattern of bulk DNA, or a single gene, in any experimental tumor not the Exhibits teach the pattern's changes caused by treatment with dMTase inhibitor. Thus the rejection is sustained.

Further, in their Remarks on page 9 Applicants argue that because they described assays that methylated DNA is demethylated in the presence of DNA demethylase, there is not lack of written description for alteration of a methylation pattern of DNA and that one of skill in the art would realize that the inventors had possession of the claimed invention at the time the application was filed.

Applicant's argument has been fully considered, but is found not persuasive for the following reasons. The argument refers to the measurements of catalytic activity of dMTAse, wherein the substrate is any methylated DNA molecule including oligonucleotides or plasmid. Measurements of catalytic activity of demethylase is not the same as demonstrating a change in the methylation pattern of the DA of an entire cell. The pattern of DNA methylation shows a sequence of DNA with particular cytosines methylated. To show the methylation pattern and its changes experimentally

one has to show sequencing gels with some C positions methylated and other not methylated or at least results of such sequencing. Thus the rejection is not withdrawn.

On page 10 and 11 Applicants argue that they disclosed a range of dMTAse inhibitors, including MTA as disclosed in Exhibit D from Rule 132 Declaration, and "additional inhibitors could be determined by routine experimental techniques known to one of skill in the art and no undue burden would be placed on one of skill in the art to determine additional inhibitors." Applicant's argument is found not persuasive, for the following reasons. The inhibitors were not the subject of rejection for lack of scope of enablement, because, indeed, one of skill in the art can determine whether a candidate chemical is a dMTA inhibitor. This is the lack of written description for which claim 32 and 36 have been rejected.

In the last paragraph on page 11 Applicants indicate that claim 36 has been amended to be directed to a method wherein altering the methylation pattern silences a gene.

> "As known in the prior art, for example see the review by Szyf (2003, Drug Resistance Updates, section 5, as Exhibit E:'silencing of tumor suppressor genes by hypermethylation is well documented'; and page 1, lines 9-15 of the present application: altering a methylation pattern causes differential gene expression. One of skill in the art would realize and would be able soundly predict based on the teaching of the present disclosure that inhibition of demethylase would promote methylation of a

gene, which in turn would silence the gene. Further, no undue burden would be placed on one of skill in the art to arrive at amended claim 36. In further support of this amendment, Applicants attached herewith additional experimental data, in the aforementioned Rule 132 Declaration (Exhibit D), showing that anti-sense inhibition of DNA demethylase (SEQ ID NO: 1) prompts inhibition (silencing) and remethylation of uPA, including Herman et al. (1996) Proc. Natl. Acad. Sci. USA, 93: 9821-9826."

Applicant's arguments have been thoroughly considered but are found not persuasive for the following reasons. The arguments are based on the assumption that any silencing of any gene is related to inhibition of tumor growth. This, however, is not true. By remethylation of activated oncogenes one may cause inhibition of tumor growth, however by silencing tumor suppressors one may promote tumor growth and accelerate metastasis. As to no undue burden placed on one of skill in the art to arrive at amended claim 36, one skilled in the art has to know which gene(s) is to be remethylated, i.e. which gene dominates in the tumor phenotype at hand and how one targets the methylation to the appropriate gene. Thus in addition to lack of written description claim is rejected for lack of enablement.

The examiner acknowledges Rule 132 Declaration's data showing that anti-sense inhibition of dMTAse promotes silencing and remethylation of GFP and uPA. These data are obtained obtained five years after filling the PCT application of which the

current application is a national stage. The data consist a new matter, because the GFP and uPA are not mentioned in the specification and claims as filed. Thus, the filed Rule 132 Declaration is not persuasive and rejection is maintained.

Acknowledging elegant experiments with GFP gene, which have shown that inhibition of dMTase prevents demethylation of GFP, when this gene is transfected into HEK293 human cells, the examiner emphasizes that these data are not directly related to invention as claimed in claim 36, because GFP does not play any role in human tumorigenesis. On the other hand, uPA gene is directly related to the invention as claimed in claim 36. However, even if said gene were mentioned in the disclosure as filed, it did do not meet requirements of written description because uPA gene does not posses characteristic features identifying any gene in mammalian genome that is to be silenced by inhibition of dMTAse, i.e. uPA does not posses characteristic features of all species of the genus of genes claimed in claim 36. The scope of the claim comprises repressing tumor suppressors, which would lead to acceleration of tumor methastasis thus precluding practicing the invention as intended.

3.2. 35 USC section 112, first paragraph, lack of written description

On page 13, in support of enablement of the claimed invention Applicants turn examiner's attention to Exhibits A, B, C of Rule 132 Declaration, which are the published data that came out as a result of the present application and show that inhibition of demethylase by an antisense molecule inhibits tumorigenesis in vivo. In addition, Applicants do not believe that the claims should be limited regarding an

antagonist or inhibitor. In summary, Applicants believe that one skilled in the art would not require undue experimentation to make the claimed invention.

Applicants' arguments have been fully considered but are found not persuasive, because the Declaration presents data obtained many years after filing the instant application and refers to tumor cells, genes, and inhibitors that mostly are not mentioned in the instant application.

In conclusion the claims remain rejected for the reasons indicated above.

3.3. *35 USC section 112, first paragraph, lack of enablement*

Traversing Examiner's rejection of Claims 32-36, Applicants argue that the phrase "a methylation pattern in DNA" is commonly known and understood in the art and page 31, line 5 to page 32 line 25 shows a method to measure and visualize the pattern of DNA methylation and how to alter it with demethylase.

As indicate above in rejection for lack of written description and enablement Applicants do not teach in the specification how to visualize change in DNA methylation pattern in bulk DNA or in a particular gene. Therefore the rejection is maintained.

4. Conclusion

No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Patent Examiner
Art Unit 1652

1605